Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

Monica K. Lachey

Date

Addressing rotavirus vaccination missed opportunities using the National Immunization Survey

By

Monica K. Lachey Master of Public Health

Department of Epidemiology

Robert A. Bednarczyk, PhD

Thesis Committee Chair

Evan Anderson, MD

Thesis Committee Member

Walter Orenstein, MD

Thesis Committee Member

Addressing rotavirus vaccination missed opportunities using the National Immunization Survey

By

Monica K. Lachey B.S. The Ohio State University 2013

Thesis Committee Chair: Robert A. Bednarczyk, PhD

An abstract of

A thesis submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degree of Master of Public Health in Epidemiology

2015

Abstract

Addressing rotavirus vaccination missed opportunities using the National Immunization Survey By: Monica Lachey

Background: In the United States, rotavirus vaccine (RV) coverage has plateaued below that of other infant vaccines. In 2013, the World Health Organization (WHO) expanded global recommendations for age at RV administration, but the US age restrictions remain unchanged. We assessed missed opportunities for RV series initiation and explored hypothetical increases in RV coverage if current age restrictions were expanded.

Methods: Data from the 2009 and 2012 National Immunization Survey (NIS) were analyzed to assess adherence to ACIP recommendations for 6 infant vaccines. We assessed missed opportunities for RV initiation using diphtheria, tetanus, and acellular pertussis vaccine (DTaP) as a marker of received vaccinations. Additionally, we calculated the hypothetical increase in RV coverage if current RV age restrictions were expanded, accounting for potential missed opportunities outside the current RV administration window.

Results: Of 17,053 children in the 2012 cohort, only 83% received at least 1 dose of RV. Of these children 95% received RV within the ACIP recommended timeframe. Interestingly, of the 17% of children who did not receive RV, nearly 15% received >= 1 dose of DTaP. If RV were administered to all children with missed opportunity for RV administration, an additional 845,894 children would receive >= 1 dose RV, resulting in 97% initiation.

Conclusions: Addressing missed opportunities and expanding the recommendations for RV administration could increase RV initiation to levels seen in other infant vaccines. Increased coverage provides direct benefit to vaccinated children and is important in providing indirect protection to unvaccinated children and adults, decreasing disease incidence.

Addressing rotavirus vaccination missed opportunities using the National Immunization Survey

By

Monica K. Lachey B.S. The Ohio State University 2013

Thesis Committee Chair: Robert A. Bednarczyk, PhD

A thesis submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degree of Master of Public Health in Epidemiology 2015

Table of Contents

Introduction
Methods
Study population
Data Analysis
Ethics5
Results
Study population
Adherence to vaccine recommendations for series initiation
Missed Opportunity for Rotavirus Vaccination7
Sensitivity analysis of rotavirus vaccine coverage with hypothesized increases in
rotavirus vaccine uptake among children with missed
opportunity
Discussion
Conclusions
References
Tables and Figures

Introduction

Rotavirus is a leading cause of gastroenteritis in infants and young children in the United States and worldwide. Prior to vaccine licensure, rotavirus accounted for an estimated 55,000 - 70,000 US hospitalizations per year among children <5 years at a cost of approximately \$1 billion in direct and indirect costs (1).

Two live oral rotavirus vaccines (RV) are currently available for administration in the United States. A pentavalent vaccine (RV5), FDA licensed in 2006, is given in 3 doses and a monovalent vaccine (RV1) was licensed in 2008 and is administered in 2 doses. The Advisory Committee on Immunization Practices (ACIP) recommends that the first dose vaccine be administered at 2 months. Although doses are ideally administered at 2 month intervals, a minimum interval of 4 weeks between doses is recommended. The minimum age for initiation of any rotavirus vaccine series is 42 days, and the first dose of rotavirus vaccine must be administered before 15 weeks of age (2). The maximum age for any dose of rotavirus vaccine is eight months and 0 days (2).

Although rotavirus vaccination rapidly increased immediately following FDA licensure to 67.3% in 2011, vaccination rates have plateaued well below the US Department of Health and Human Services (HHS) Healthy People 2020 goals of 80% complete vaccination coverage (3). In 2013, the Centers for Disease Control and Prevention estimated that only 72.6% of eligible US children ages 19-35 months had received at least two doses of any rotavirus vaccine (4). Of all thirteen diseases against which children are recommended to be vaccinated routinely in a fixed schedule in the United States during the first two years of life, only the hepatitis A (HepA) vaccine (54.7%) had lower complete vaccination coverage than rotavirus (4). Reasons for low coverage have been attributed to a wide array of factors including financial and administrative burden, safety concerns, and complexity of the rotavirus vaccine schedule (5, 6).

In 2013, the World Health Organization (WHO) lifted strict recommendations for rotavirus vaccination schedules to reduce mortality by allowing a more flexible vaccine schedule (7). The WHO now recommends administration of RV with DTaP vaccine up to 24 months of age (7). The RV schedule has remained unchanged in the United States and the lack of opportunities for catch-up vaccination may contribute to the low rotavirus rates of US rotavirus vaccination. This study explores the potential for increased rotavirus vaccine coverage if current restrictions were lifted in the United States.

Using data from a national dataset of over 30,000 children, we investigated the determinants of rotavirus vaccine initiation and implications of removing vaccination schedule limitations from the rotavirus vaccine by quantifying missed rotavirus vaccination opportunities.

Methods

Study population

We analyzed 2009 and 2012 data from the National Immunization Survey (NIS). The NIS datasets are compiled through utilization of a list-assisted random-digit dialing telephone survey of parents or guardians, followed by a mailed survey to respondent's immunization providers for vaccination verification (8). The study population is comprised of children aged 19-35 and living in the United States at the time of survey. Children who received their initial rotavirus vaccine after the time of the survey were excluded from analyses to remove bias introduced by vaccination following the interview.

Data Analysis

Data analysis was performed using SAS 9.4 (Cary, NC). SAS procedures specific to complex survey design analysis were used with sampling weights as provided in the Data User's Guide for the NIS-Child datasets (2009-2012) (8).

We used ACIP recommendations for vaccine administration to assess timeliness of rotavirus vaccination. Administration of the first dose of rotavirus vaccine between 42 and 104 days of age, inclusive, was considered to be in accordance with ACIP recommendations. Rotavirus vaccine administration of dose 1 before 42 days of age or after 93 days of age was considered to be outside of the ACIP recommendations. The proportion of children with rotavirus vaccine within and outside of the ACIP

recommendations were computed, and compared by child, maternal, socioeconomic, and health care provider covariables.

The mean and median age at first dose of vaccination was calculated for each of six common infant vaccines (Diphtheria and Tetanus toxoids and acellular Pertussis [DTaP], hepatitis B [HepB], *Haemophilus influenzae* type b [Hib], poliovirus [IPV], pneumococcal conjugate vaccine [PCV], and rotavirus [RV]). The proportion of children who initiated each respective vaccine was determined. Initiation of a vaccine was defined as receiving at least one dose of the selected vaccine. Of the children who initiated the vaccine, we calculated the proportion of children who initiated within the ACIP recommended time window for dose 1 of rotavirus vaccine.

We identified children with missed opportunities for rotavirus vaccination. Due to high correlation of age at administration of first dose of all the common infant vaccines, we used DTaP as the comparison vaccine for missed opportunities. For our study, a missed opportunity was defined as administration of first dose of DTaP vaccine series without initiation of rotavirus vaccination. We further explored missed opportunity by distinguishing between DTaP receipt occurring during the recommended window for rotavirus vaccine initiation, and outside of the recommended vaccination window for either vaccine (before 42 days of age or after 93 days of age).

We used bivariate logistic regression analysis to assess the association between child, maternal, socioeconomic, and health care provider variables that may be associated with rotavirus vaccine initiation. Unadjusted odds ratios were calculated for 0 doses of rotavirus vaccine and for missed opportunities for RV initiation. The Wald confidence interval was reported for each point estimate with an alpha of 0.05.

All potential predictors of rotavirus vaccination initiation or missed opportunities for rotavirus vaccine administration were selected *a priori*. Child demographic variables included age, race/ethnicity, gender, firstborn status, and number of children < 18 living in the household. Maternal demographic variables included maternal age, marital status, and maternal education. Socioeconomic variables included poverty status (based on previous year Census poverty thresholds), health insurance category, and whether the child was uninsured at any point prior to the survey date. Provider variables of interest included provider facility type, location of provider vaccine order, and whether the child's providers reported vaccination to an immunization registry.

We conducted a sensitivity analysis to assess hypothetical increases in RV uptake among children who did not receive RV and had missed opportunities, using SAS PROC SURVEYFREQ.

Ethics

This study describes a secondary analysis of de-identified, publically available datasets and was considered exempt from IRB human subject review by the Emory Institutional Review Board.

3. Results

Study population

We used provider verified data, yielding 17,053 children and 16,687 children from the 2009 and 2012 datasets, respectively.

Adherence to vaccine recommendations for series initiation

In the 2012 cohort, only 82.9% (CI = 82.8, 84.0) of children initiated the rotavirus vaccine series, the lowest initiation percentage of any of the infant vaccines; by comparison, 97.4% (CI = 97.0, 97.9) of children initiated the DTaP vaccine series. The median age for series initiation of rotavirus vaccine, defined as receipt of first dose of vaccine series, was 63.2 days (IQR: 60.6-69.9) and the mean for rotavirus initiation was 69.2 days [Table 1]. Each of the other 6 common infant vaccines were initiated with a median of 63-65 days.

Of children who received RV, 95.1% (CI = 92.1, 93.8) received the first dose within the ACIP recommendations of 42-104 days. This is 5% higher than the proportion of children receiving DTaP vaccine between 42 and 93 days of age in adherence to ACIP recommendations for DTaP administration (90.1%, CI = 89.3, 91.0) [Figure 1]. Additionally, of children receiving at least 1 dose of DTaP, 92.5% (CI = 91.8, 93.3) received the first dose of DTaP between ages 42-104 days, the recommended timeframe for RV vaccine initiation. The majority of infants who were not vaccinated within the recommended time frame received the first dose of the RV series after the maximum acceptable age instead of before the acceptable age.

Of all the child, maternal, socioeconomic, and provider characteristics assessed, only provider facility type and number of children in household under 18 years of age was significantly associated with rotavirus vaccine initiation [Table 2]. Children served by private providers were significantly more likely to initiate rotavirus vaccination than those served at public clinics. Of children whose vaccination provider was identified as private provider facility, the odds of no rotavirus vaccine initiation was 0.6 (CI = 0.5, 0.8), compared to children who's vaccinating provider facility is characterized as a public provider facility. Additionally, having more children in the household was associated with a lower risk of starting rotavirus vaccination. When comparing RV among children with 4 or more children under the age of 18 in the household, the odds of no rotavirus vaccine initiation was 1.4 (CI = 1.1, 1.9) compared to those with only 1 child in the household.

Missed Opportunity for Rotavirus Vaccination

The proportion of children who did not receive any doses of rotavirus vaccine decreased from 43.9% (CI = 42.5, 45.2) in 2009 to 17.1% (CI = 16.0, 18.2) in 2012 [Figure 2]. In the 2012 cohort, 14.6% (CI = 13.5 - 15.6) of children did not receive rotavirus, but received >= 1 dose of the DTaP vaccine. Nearly 2.5% of children in 2012 received did not receive any doses of DTaP and rotavirus vaccines, an equivalent of 145,151 children. Of all children in the 2012 cohort, 9.9% (CI = 9.1, 10.8) of children received DTaP during the recommended timeframe for rotavirus vaccine administration, but did not receive a dose of rotavirus vaccine. Additionally, 4.6% (CI = 4.0, 5.3) of children received DTaP outside of the recommended time frame for rotavirus administration. In assessment of the 2012 cohort, households reporting 4 or more children under 18 years of age compared to households with only one child was associated with increased odds for missed opportunities for RV receipt (OR=1.4, CI=1.1, 1.9) [Table 2]. Hispanic children had decreased odds of missed opportunities, compared to non-Hispanic white children (OR=0.7, CI=0.5, 0.8).

Sensitivity analysis of rotavirus vaccine coverage with hypothesized increases in rotavirus vaccine uptake among children with missed opportunity

Vaccine series initiation for DTaP was 97.4% in the 19-35 mo 2012 cohort. This is nearly 15% higher than RV series initiation, 82.9%, in 2012 [Table 1]. We investigated the hypothetical increase in total RV vaccine coverage if dose 1 of RV was to be administered with the first dose of DTaP among children with missed opportunities [Table 3]. Missed opportunities for RV were assessed for first doses of DTaP administered prior to age at interview, no later than 35 months of age. If RV were to be administered to 100% of children receiving DTaP during the RV recommended time frame (42-104 days of age), we estimated an additional 576,712 children would receive at least 1 dose of RV. This increases the total RV initiation from 83% to 93% of the total 19-35 mo 2012 cohort. If RV were to be administered to 100% of children receiving DTaP outside the RV recommended timeframe an additional 269,182 children would receive at least 1 dose of RV, resulting in 97% initiation of RV.

Discussion

Our study showed substantial opportunity for improving rotavirus vaccine rates. As rotavirus vaccine coverage rates have stagnated well below the Healthy People 2020 goals of 80%, barriers to rotavirus vaccine administration have shifted (3). Financial and logistic barriers to vaccine administration have declined, but providers now cite parental and provider safety concerns and reluctance to include another vaccine as primary reasons for non-vaccination (9). Persisting safety concerns related to the intussusception risk associated with the first manufactured rotavirus vaccine have resulted in strict adherence to ACIP recommendations (5, 6, 9). Of first RV doses administered to the 2012 NIS cohort, 95% were given in the recommended interval [Table 1]. Additionally, several recent studies have highlighted the increasing trend in parental desires for delayed or alternative vaccine schedules (11-12). Vaccine hesitancy and alternative vaccine schedules may limit the opportunity for improving RV vaccination beyond current coverage rates.

Several studies in Mexico and Brazil have demonstrated that the direct and indirect benefits of rotavirus vaccination outweigh any risk of intussusception associated with late administration of rotavirus vaccine (13-19). In 2013, in response to these and other data, the World Health Organization (WHO) recommended expanding rotavirus administration to coincide with administration of DTaP, regardless of age, to include children previously excluded by conventional age restrictions of rotavirus vaccine administration (7). However, the United States has not yet modified their recommendations.

Our results show that a similar approach in expanding the recommendations for rotavirus vaccination could increase initiation of rotavirus vaccination in the United States by as

much 6 percentage points or an additional 269,182 children. Because rotavirus vaccine administration is highly correlated with DTaP vaccine administration among children, we used DTaP as a marker for missed opportunities for rotavirus administration. If all missed opportunities for rotavirus vaccination were taken, defined as DTaP administered during the rotavirus window with no rotavirus administration, approximately 576,712 additional children would receive at least 1 dose of rotavirus vaccine (93% rotavirus series initiation) [Table 3]. Assuming all missed opportunities for rotavirus vaccination were taken, approximately 845,894 additional children in the 19-35 month cohort in 2012 would have received the first dose of rotavirus vaccine. This would result in 5,661,780 children of the 5,807,170 million children in this age group, 19 to 35months receiving at least 1 dose of RV, or 97% RV series initiation [Table3]. Increasing coverage to the unvaccinated population by addressing missed opportunities is important in expanding protection against rotavirus disease. Similar to that of other vaccines (e.g., PCV), rotavirus vaccination has not only resulted in direct protection of vaccinated children but also indirect protection (herd protection) of unvaccinated children and adults, reducing overall incidence of rotavirus disease (20-24). This is particularly important in that the only characteristic to be significantly associated with both failure to initiate RV and missed opportunities for RV was children living in households with at least 4 children. These children are particularly important as they have increased contact with other susceptible children. Thus, maximizing protection of children and adults by increasing coverage among vaccine-eligible children is important.

The analyses described in this study have several limitations. The NIS Child data for 2013 was not available at time of analysis; therefore our analyses are limited to data

through 2012. Because we used publically available national datasets, our analyses were limited to the aggregate variables available in the dataset. We assessed coverage according to vaccine initiation and did not consider completion in our analyses due to different dose vaccine series (RV1 and RV5). We did not distinguish between RV1 and RV5 vaccine administration; however, we expect our results are not greatly impacted because we focused the analyses on initiation and not completion of RV series, which may be impacted by specific formulations. We only looked at rotavirus vaccine initiation potential and did not review how many children would have completed the recommended vaccination series. Finally, additional research should be conducted to look into specific socio-economic factors that may be of importance in developing targeted strategy for increasing rotavirus coverage.

Conclusions

Our results support expanding rotavirus vaccine administration recommendations to increase coverage. This study highlights the need to further investigate safety and efficacy of rotavirus vaccination in the United States among children vaccinated outside of the current ACIP recommended age. The Vaccine Safety Datalink has provided data for several analyses of rotavirus safety, and could be used to evaluate the safety of RV administration among older children (25, 26). Successful increases in coverage following introduction of the two currently available rotavirus vaccines provide hope that if these strict recommendations were to be lifted, rotavirus vaccination coverage could reach the high levels of coverage seen in other infant vaccine series and achieve Healthy People 2020 goals. Continued targeted education is necessary to inform providers and parents of the potential direct and indirect benefits of rotavirus vaccination for their children and families.

References

1. Tucker AW, Haddix AC, Bresee JS, Holman RC, Parashar UD, Glass RI. Costeffectiveness analysis of a rotavirus immunization program for the United States. JAMA. 1998;279(17):1371–1376

2. Centers for Disease Control and Prevention (2009). Prevention of Rotavirus Gastroenteritis Among Infants and Children Recommendations of the Advisory Committee on Immunization Practices (ACIP). Available from <u>http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5802a1.htm</u>.

3. U.S. Department of Health and Human Services (2012) Healthy People 2020 topics and objectives. Available from <u>https://www.healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases</u>.

 CDC. National, State, and Selected Local Area Vaccination Coverage Among Children Aged 19–35 Months — United States, 2013. MMWR 2014; 63(34): 741-748.

5. Kempe A, Patel MM, Daley MF, et al. Adoption of rotavirus vaccination by pediatricians and family medicine physicians in the U.S. Pediatrics 2009;124(5):e809–e816

6. O'Leary ST, Parashar UD, Crane LA, et al. Adoption of rotavirus vaccine by U.S.Physicians: Progress and Challenges. Am J Prev Med 2013; 44(1):56-62

7. World Health Organization. Weekly epidemiological record: rotavirus vaccines WHO position paper. 2013; 88(5):49-64.

8. Centers for Disease Control and Prevention. National Immunication Survey (NIS) – Children (19-35 months). Available from <u>http://www.cdc.gov/vaccines/imz-</u> <u>managers/coverage/nis/child/</u>

9. Panozzo CA, Becker-Dreps S, Pate V, et al. Patterns of Rotavirus Vaccine Uptake and Use in Privately-Insured US Infants, 2006-2010. PLoS One. 2013; 8(9): e73825.

 Nadeau JA, Bednarczyk RA, Masawi MR, et al. Vaccinating My Way—Use of Alternative Vaccination Schedules in New York State. J Pediatrics 2015; 166(1):151-156.

11. Dempsey AF et al. Alternative Vaccination Schedule Preferences Among Parents of Young Children. Pediatrics. 2011; 128:848-856.

12. Glanz JM, Newcomer SR, Narwaney KJ, et al. A Population-Based Cohort Study of Undervaccination in 8 Managed Care Organizations Across the United States. JAMA Pediatr. 2013;167(3):274-281.

13. Patel MM et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. New England Journal of Medicine. 2011; 364:2283–2292.

14. Patel MM, Clark AD, Sanderson CF, Tate J, Parashar UD. Removing the age restrictions for rotavirus vaccination: a benefit-risk modeling analysis. PLoS Med 2012; 9:e1001330.

15. Widdowson MA, Meltzer MI, Zhang X, Bresee JS, Parashar UD, Glass RI. Costeffectiveness and potential impact of rotavirus vaccination in the United States. Pediatrics. 2007;119(4):684–697.

16. Velázquez FR et al. Postmarketing Surveillance of Intussusception Following Mass Introduction of the monovalent human Rotavirus Vaccine in Mexico. The Pediatric Infectious Disease Journal. 2012; 31:736–744.

17. Desai R, Cortese MM, Meltzer MI, et al. Potential intussusception risk versus benefits of rotavirus vaccination in the United States. Pediatr Infect Dis J 2013;32:1-7.

 Shui IM et al. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. JAMA: the Journal of the American Medical Association 2012; 307:598–604.

19. Loughlin J et al. Postmarketing evaluation of the short-term safety of the pentavalent rotavirus vaccine. The Pediatric Infectious Disease Journal 2012; 31:292–296.

20. Anderson EJ, Shippee DB, Weinrobe MH, et al. Indirect protection of adults from rotavirus by pediatric rotavirus vaccination. Clin Infect Dis. 2013; 56(6): 755-760.

21. Anderson EJ, Rupp A, Shulman ST, Wang D, Zheng X, Noskin GA. Impact of rotavirus vaccination on hospital-acquired rotavirus gastroenteritis in children. Pediatrics 2011;127:e264-70.

22. Lopman BA, Curns AT, Yen C, Parashar UD. Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. J Infect Dis 2011;204:980-6.

23. Gastañaduy PA, Curns AT, Parashar UD, Lopman BA. Gastroenteritis hospitalizations in older children and adults in the United States before and after implementation of infant rotavirus vaccination. Jama 2013; 310(8): 851-3.

24. CDC. Sustained Decrease in Laboratory Detection of Rotavirus after Implementation of Routine Vaccination – United States, 2002-2014. MMWR 2015; 64(13): 337-342.

25.Baggs J, Gee J, Lewis E et al. The Vaccine Safety Datalink: a model for monitoring immunization safety. Pediatrics. 2011;127(Supp 1):S45-S53.

	Recommended Minimum	Minimum	Maximum	Age at ad	Maximum Age at administration, day *		Initiated within		
	Age for	Acceptable	Acceptable	I		Initiated series, %	Initiated series, % recommendedations	Initiated Early *	Initiated Late*
Vaccination	Routine	Age, days	Age, days	Mean †	Age, days Mean † Median(IQR)	of total cohort (CI)	* % (CI)	%(CI)	%(CI)
Diphtheria and tetanus toxoids and									
acellular pertussis, DTaP	2	42	93	77.4	63.4(60.7-71.3) 97.4 (97.0, 97.9)	97.4 (97.0, 97.9)	90.1 (89.3, 91.0)	0.35 (0.14, 0.57)	9.5 (8.6, 10.4)
Hepatitis B, HepB (2nd dose)	2-4	28	154	93.5	64.4(59.6-100.0)	64.4(59.6-100.0) 97.1 (96.6, 97.6)	88.7 (87.8, 89.7)	0.18(0.09, 0.23)	11.2 (10.2, 12.2)
Haemophilus influenzae type b, Hib	2	42	93	<i>4</i>	63.6(60.8-72.4)	63.6(60.8-72.4) 97.3 (96.8, 97.8)	88.6 (87.7, 89.5)	$0.42 \ (0.18, 0.67)$	11.0 (10.1, 11.9)
Poliovirus, IPV	2	42	93	77.2	63.6(60.7-72.0)	96.8 (96.3, 97.3)	89.4 (88.6, 90.3)	$0.45\ (0.23, 0.69)$	10.1 (9.2, 10.9)
Pneumococcal conjugate vaccine,									
PCV	2	42	93	81.7	63.9(60.9-74.0) 96.7 (96.1, 97.2)	96.7 (96.1, 97.2)	87.0 (86.1, 88.0)	0.41 (0.18, 0.65)	12.5 (11.6, 13.5)
Rotavirus, RV	6	42	104	69.2	63.2(60.6-69.9) 82.9 (82.8, 84.0)	82.9 (82.8, 84.0)	95.1 (94.4, 95.7)	0.46 (0.14, 0.78)	4.5 (3.9, 5.1)

*Restricted to children who received >= 1 dose of respective vaccine before survey date †SD not reported for mean due to high levels of variation

|--|

Child Demographics		Study Population of total		OR (95% CI) for 0 doses RV received	Missed Opportunity DTaP administration without RV (%)	OR (95% CI) for Missed Opportunity
	10.00	20.5	140			
Age	19-23mo 24-29mo	29.7 33.9	16.3 16.5	ret 1.0 (0.8, 1.3)		ref 1.0 (0.8, 1.2)
	30-35mo	36.4	18.2	1.1 (1.0, 1.4)		1.2 (1.0, 1.4)
	50-55110	50.4	10.2	1.1 (1.0, 1.4)	15.6	1.2 (1.0, 1.4)
Race/Ethnicity	Hispanic	27.3	13.5	0.7 (0.6, 0.9)	10.9	0.7 (0.5, 0.8)
	Non-Hispanic White	47.1	18.0	ret	f 15.7	ref
	Only	47.1	10.0	101	15.7	
	Non-Hispanic Black Only	13.6	17.3	0.9 (0.8, 1.2)	14.5	0.9 (0.7, 1.2)
	Non-Hispanic Other +					
	Multiple Race	11.9	21.1	1.2 (0.9, 1.6)	18.7	1.2 (0.9, 1.7)
Gender	Male	51.2	16.8	ret		ref
	Female	48.8	17.4	1.0 (0.9, 1.2)	15.0	1.1 (0.9, 1.3)
Firstborn status of child	Yes	38.7	15.8	0.9 (0.7, 1.0)	13.6	0.9 (0.7, 1.0)
Firstborn status of child	No	61.4	15.8	0.9 (0.7, 1.0) ref		0.9 (0.7, 1.0) ref
	110	01.4	17.9	101	15.2	ier
Number of children less						
than 18 years in		27.4	16.2	ref	f 13.9	ref
Household	1					
	2 or 3	57.9	16.0	1.0 (0.8, 1.2)		1.0 (0.8, 1.2)
Maternal Demographic	>= 4	14.7	22.8	1.5 (1.2, 2.0)	18.4	1.4 (1.1, 1.9)
material Demographic	3					
Age	<=19 years	2.4	19.5	1.2 (0.7, 2.0)	15.3	1.1 (0.6, 1.9)
0	20-29 years	42.2	17.0	1.0 (0.9, 1.2)		1.0 (0.9, 1.2)
	>+30 years	55.4	17.0	ret	f 14.3	ref
Marital Status	Married	62.6	16.5	rel	f 14.2	ref
	Never	27.4	18.0	11(00.12)	15.1	11(00.12)
	Married/Widowed/Divor ced/Separated/Deceased	37.4	18.0	1.1 (0.9, 1.3)	15.1	1.1 (0.9, 1.3)
	eeu/Separaeu/Deeeuseu					
	10.17	10.0	10.6	12(10.10)	147	11/00 14
Education	< 12 Years 12 Years	19.0	18.6	1.2 (1.0, 1.6)		1.1(0.9, 1.4)
	> 12 Years > 12 Years, Non-college	27.0	18.7	1.2 (1.0, 1.5)	10.4	1.2 (1.0, 1.5)
	grad	22.3	15.9	1.0 (0.8, 1.3)	13.5	1.0 (0.8, 1.2)
	College grad	31.6	15.5	ret	f 13.7	ref
Socio-economic Variable	es					
Poverty status (based on						
2011 Census poverty		26.4	16.1	ret	14.0	ref
thresholds)	Above Poverty, >\$75K					
	-	34.9	16.4	1.0 (0.8, 1.2)	14.0	1.0 (0.8, 1.2)
	Above Poverty, <=\$75K			1.0 (0.8, 1.2)		1.0 (0.8, 1.2)
	Below Poverty	38.7	17.6	1.1 (0.9, 1.4)	14.7	1.1 (0.9, 1.3)
T T T T T T T T T T	v	0.5	15.0	10 (0 7 1 0)	14.0	10(07.12)
Uninsured at any point	Yes No	9.5 90.5	15.9 16.6	1.0 (0.7, 1.2) ref		1.0 (0.7, 1.3) ref
Provider Characteristic		70.5	10.0		14.5	lei
Provider facility type	All public facilities	12.2	20.7	ret		ref
	All hospital facilities	11.4	22.6	1.1 (0.8, 1.5)		0.8 (0.6, 1.1)
	All private facilities	58.1	14.4	0.6 (0.5, 0.8)		0.7 (0.5, 0.9)
	All military/other facilities Mixed	2.1 16.1	16.4 16.0	0.8 (0.4, 1.3) 0.7 (0.5, 1.0)		0.7 (0.4, 1.1) 0.7 (0.6, 1.0)
	WIXed	10.1	10.0	0.7 (0.5, 1.0)	14.0	0.7 (0.0, 1.0)
Providers order vaccines						
from state/local health		80.3	15.9	ret	f 14.9	ref
department	All providers					
	Some but possibly or	8.5	15.3	1.0 (0.7, 1.3)	14.8	1.0 (0.7, 1.3)
	definitely not all providers	11.2	17.2	1.1 (0.9, 1.4)	15.2	10(0812)
	None of the providers	11.2	17.2	1.1 (0.9, 1.4)	13.2	1.0 (0.8, 1.3)
Providers reported child's						
vaccintations to		70.8	15.5	rel	f 14.4	ref
Immunization registry	All providers					
	Some but possibly or	9.4	15.7	1.0 (0.8, 1.4)	15.3	1.1 (0.8, 1.4)
	definitely not all providers		167	11/00 14	145	10/00 12
	None of the providers	19.8	16.7	1.1 (0.9, 1.4)	14.5	1.0 (0.8, 1.3)

	Additional % of children receive >=1 dose RV	# Additional children, >= 1 dose RV	Total children, >=1 dose RV received	% Total RV Initiation*
Baseline RV coverage, >=1 dose received	-		4,815,886	83%
Hypothesized overall RV initiation assuming X% of RV uptake among children with missed opportunity who received DTaP within the recommended RV timeframe	10% 25% 50% 75% 100%	54,007 135,017 270,033 432,534 576,712	4,869,893 4,950,903 5,085,919 5,248,420 5,392,598	84% 85% 88% 90% 93%
Hypothesized overall RV initiation assuming X% of RV uptake among children with missed opportunity who received DTaP outside the recommended RV timeframe	10% 25% 50% 75% 100%	30,778 76,945 153,890 230,835 269,182	4,846,664 4,892,831 4,969,776 5,046,721 5,085,068	83% 84% 86% 87% 88%
Hypothesized overall RV initiation assuming combined increases in RV uptake among children with missed opportunity, (% received DTaP within recommended RV timeframe / % received DTaP outside recommended RV timeframe)	10%/10% 10%/25% 10%/75% 25%/25% 25%/25% 25%/75% 50%/75% 75%/75% 75%/100%	84,785 130,952 207,897 284,842 211,962 288,907 365,852 423,923 500,868 634,421 701,716	4,900,671 4,946,838 5,023,783 5,100,728 5,027,848 5,104,793 5,181,738 5,239,809 5,316,754 5,450,307 5,517,602	84% 85% 87% 88% 87% 88% 89% 90% 92% 94% 95%

Table 3. Sensitivity analysis of Rotavirus vaccine coverage with hypothesized increases in Rotavirus vaccine uptake among children with missed opportunity, NIS Child 2012

*Coverage is calculated according to an estimated 5,807,170 children in the US cohort aged 19-25 mo, NIS Child 2012



Figure 1. Average day of vaccine initiation, NIS 2009 and 2012. Dashed vertical lines are placed at 42 days and 104 days, the recommended minimum and maximum age for first dose of RV. The red and blue lines represent the normal distribution of day of DTaP and RV dose 1 administration, respectively.



Figure 2a. Rotavirus vaccine initiation and missed opportunity in 2009 and 2012, NIS Child. The figure displays the distribution and timeliness of rotavirus vaccine (RV) initiation and missed opportunities for rotavirus initiation among the 2009 and 2012 National Immunization Survey cohorts, ages 19-35 months. Missed opportunity for RV initiation, highlighted in the gray shaded boxes, is defined as \geq 1 dose DTaP without administration of first dose of RV.



Figure 2b. Rotavirus vaccine initiation and missed opportunity in 2009 and 2012, NIS Child. The figure displays the distribution and timliness of rotavirus vaccine (RV) initiation and missed opportunities for rotavirus initiation among the 2009 and 2012 National Immunization Survey cohorts, ages 19-35 months. Missed opportunity for RV initiation, highlighted in gray shaded boxes, is defined as \geq 1 dose DTaP without administration of first dose of RV.